

EXHIBIT C

Antiepileptic drugs and risk of suicide: a nationwide study

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SUMMARY

Purpose Patients with epilepsy or psychiatric diseases have increased risk of suicide, but whether the risk is influenced by antiepileptic drug (AED) treatment is unclear. Studies have suggested that AEDs in general increase the risk of suicidal behaviour shortly after initiation. This study investigated possible differences in suicide risk associated with different AEDs.

Methods The use of AEDs in the Danish population from 1997 to 2006 was determined by prescription claims. The risk of suicide associated with use of AEDs was estimated by case-crossover analyses, where each case serves at its own control during different periods. For sensitivity, the risk of suicide was estimated by a time-dependent Cox proportional-hazard analysis in AED treatment-naïve patients.

Results There were 6780 cases committing suicide in the 10-year study period, of which 422 received AED treatment at the time of suicide. The case-crossover analysis estimated AED treatment initiation to increase the risk of suicide (odds ratio (OR): 1.84, 95% confidence interval (CI): 1.36–2.49). Clonazepam (OR: 2.01, CI: 1.25–3.25), valproate (OR: 2.08, CI: 1.04–4.16), lamotrigine (OR: 3.15, CI: 1.35–7.34) and phenobarbital (OR: 1.96, CI: 1.02–3.75) were associated with a significant increased risk, while the remaining examined AEDs did not significantly influence the risk. In the cohort comprising of 169 725 AED treatment-naïve patients, the Cox proportional-hazard analysis yielded similar results.

Conclusions This study suggests that clonazepam, valproate, lamotrigine and phenobarbital relatively shortly after treatment initiation may increase the risk of suicide. The increased risk of suicide associated with these AEDs appears to be a consistent finding. Copyright © 2010 John Wiley & Sons, Ltd.

KEY WORDS—antiepileptics; suicide; epilepsy; AED

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INTRODUCTION

Patients with epilepsy and/or psychiatric disorders have an increased risk of committing suicide.^{1–6} However, it is uncertain whether the association between these diseases and suicidal behaviour is due to the baseline neurological disease and co-morbidities, or if antiepileptic drug (AED) treatment is a contributing risk factor.^{7,8} In January 2008, the U.S. Food and Drug Administration (FDA) issued a general alert on the possible increased risk of suicide associated with AEDs.⁷ This alert was based on a

meta-analysis of 199 placebo-controlled clinical studies of 11 different AEDs. In order to investigate potential differences in suicidal risk caused by individual AEDs, we conducted a nationwide register-based study covering 4.6 million individuals. AEDs are used for both epilepsy and psychiatric disorders, and in the current study, patients treated with AEDs for any therapeutic indication were examined.

METHODS

Databases

In Denmark all citizens have a unique and permanent personal civil registration number which enables linkage

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of information between national administrative registers on an individual level. The Danish Register of Medicinal Product Statistics (National Prescription Register) holds information on all prescriptions dispensed from Danish pharmacies since 1995. All dispensed drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification. The register keeps information about the date of dispensing as well as dispensed drug formulation, strength and quantity. Pharmacies in Denmark are required to register all dispensed prescriptions due to partial reimbursement of drug expenses by the national healthcare system, and complete and accurate registration of all drug prescriptions in this register has previously been validated.⁹ The Danish National Patient Register holds information on all patient admissions and diagnoses to Danish hospitals since 1978. At discharge each hospitalization is registered by one primary and, if appropriate, one or more secondary discharge diagnoses according to the International Classification of Diseases; until 1994 according to the 8th revision (ICD-8) and after 1994 the 10th revision (ICD-10). The civil registration system holds information on vital status for all citizens, with all deaths being registered within 14 days of occurrence. The National Causes of Death Register holds information on primary and contributing causes of death. The Integrated Database for the Danish Labour Market provides information on income, education and socioeconomic status.

Study population

The study population comprised all Danish citizens alive and aged ≥ 10 years on 1 January 1997. Dispensing data for AEDs in the study period from 1 January 1997 to 31 December 2006 were obtained from the National Prescription Register. Suicides were identified from the National Causes of Death Register as ICD-10 codes: X60–X84.

Medical treatment

AED treated patients were identified if they claimed one of following prescriptions (ATC codes): phenobarbital (N03AA02), primidone (N03AA03), phenytoin (N03AB02), clonazepam (N03AE01), carbamazepine (N03AF01), oxcarbazepine (N03AF02), valproate (N03AG01), tiagabine (N03AG06), lamotrigine (N03AX09), topiramate (N03AX11), gabapentin (N03AX12), levetiracetam (N03AX14), zonisamide (N03AX15), pregabalin (N03AX16) or clobazam (N05BA09). Treatment periods were calculated for each AED by dividing the number of tablets dispensed

with the estimated daily dosage. The estimated daily dosage for each individual was calculated by comparing the cumulated dosage and the elapsed time between seven successive prescriptions for the same AED, as described in details previously.¹⁰ If less than seven prescriptions for the same AED were available for a patient, the accepted standard daily therapeutic dosage for the individual agent was used in order to calculate lengths of exposed and unexposed periods. To adjust for patients with lower daily dosages than anticipated we defined all treatment breaks less than 60 days as being in-treatment periods.

Co-morbidity and socioeconomic status

As a measure of co-morbidity we used Charlson's Comorbidity Index, modified for ICD-10.^{11–13} To further enhance the discriminative power of the index we included patient diagnoses obtained up to 1 year before the first AED prescription claim. To account for psychiatric diseases potentially related to the indication for AED treatment we defined a psychiatric covariate. Data on diagnoses of psychiatric- or behavioural disorders (ICD-8: 290–315, ICD-10: F00–F99) prior to the first AED prescription claim were gathered from the Danish National Patient Register. Furthermore, we obtained information from the National Prescription Register on baseline use, i.e. 1 year up to first AED prescription claim, of concomitant medication for the following drugs (ATC code): antidepressants (N06A), antipsychotics (N05A) and anxiolytics (N05B). Information on epilepsy (ICD-8: 345, ICD-10: G40–G41) diagnosed prior the first AED prescription claim was obtained from the Danish National Patient Register. To account for the possibility of AEDs being used as an adjunct to concomitant analgesic therapy we identified patient use of opiate analgesics (ATC: N02A) from the National Prescription Register. If a prescription on opiate analgesics was claimed ≤ 180 days before the first AED prescription claim the patient was categorized as using AED for analgesic treatment. Socioeconomic status was defined by the individual average yearly gross income during a 5-year period from 1992–1996. Patients were divided into tertiles according to their income, as described previously.¹⁴ Information on civil status, i.e. living alone or not, was obtained for the year of first AED prescription.

Statistical analyses

To examine the risk of suicide associated with AEDs we used a case-crossover model where only individuals with an event are included in the analyses. The case-

crossover method is based on the case-base paradigm, but instead of using matched controls, every individual is used as its own control during different time periods before the event. A time period of 30 days prior to the suicide was chosen as the case period, and to enhance the strength of the analyses we included two control periods. The control periods selected were from 120 to 90 days and from 90 to 60 days prior to the suicide. If a patient was found to have used a specific AED for even 1 day in a given period, the patient was considered exposed to the AED in the whole period.¹⁵ As the patient serves as its own control in other periods, this eliminates the effect of unmeasured chronic confounders. AEDs were first entered in the analyses as one single group for estimation of an overall risk, and then analyzed individually as separate drugs.

To consolidate our results, we performed a historical cohort study on treatment naïve patients. Treatment naïve patients were defined as patients initiating AED treatment between 1997 and 2006 and not receiving any AED in 1996. The patient inclusion date was the day of first claimed prescription of an AED. Patients were followed until 31 December 2006 or until date of death. The risk associated with initiation of AED treatment was estimated by Cox proportional-hazard analysis. Treatment periods were entered as time-dependent covariates, i.e. patients were only considered at risk when they were exposed to the drug. Monotherapy with carbamazepine was chosen as the reference, because carbamazepine, a traditional AED with wide indications is one of the most commonly used AEDs and has a neutral effect on the risk of suicide according to the case-crossover analyses. Hazards associated to the use of AEDs in different time

intervals were estimated. The time intervals analyzed were the first 30, 90 and 180 days after initiation of a new AED treatment. The Cox model was adjusted for age, gender, socioeconomic status, Charlson's score, psychiatric covariate, concomitant medication, analgesic covariate, diagnosis of epilepsy and civil status. The proportional-hazard assumption, linearity of continuous variables and lack of interactions were found to be valid unless otherwise indicated.

All statistical analyses were performed with SAS, version 9.1 (SAS Institute Inc., Cary, NC, USA).

Ethics

No ethical approval is required for retrospective register studies in Denmark. The study was approved by The Danish Data Protection Agency (No. 2003-54-1269).

RESULTS

Case-crossover analyses

There were 6780 registered suicides in the entire population in the 10-year study period. Mean age was 54.0 years (\pm standard deviation (SD): 18.7) and men comprised 72.1%. Of the 6780 cases, 898 used AEDs in the period, 422 were receiving AED treatment at the time of suicide and 365 (86%) were only receiving one AED at this specific time. All 6780 cases were included in the case-crossover analyses; the respective proportions of patients in-treatment in the control and case periods and the results of the analyses are shown in Figure 1. Overall, AED use increased the risk of committing suicide with an odds ratio (OR) of 1.84

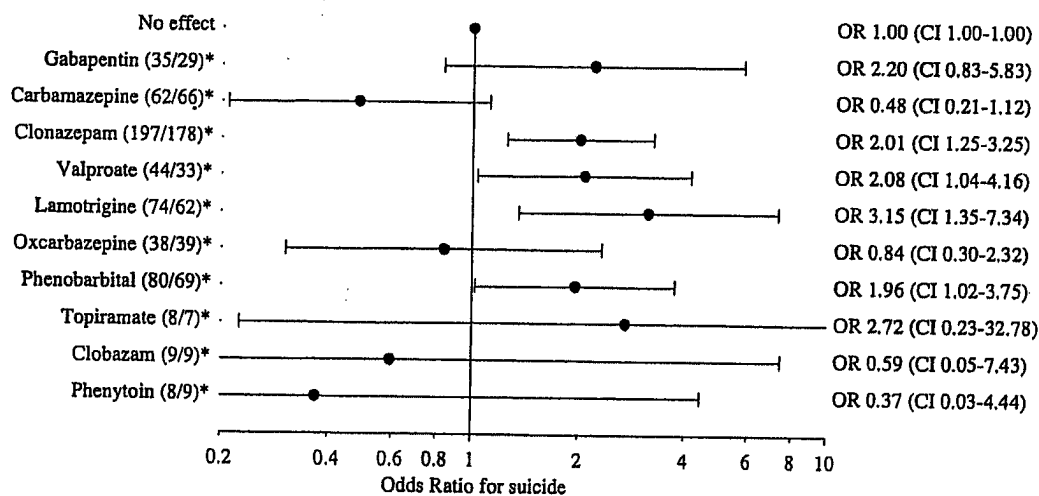


Figure 1. Results of the case-crossover analyses. The case period was day 0–30 prior to the suicide. The control periods were day 90–120, and day 60–90, prior to the suicide. *(Number treated in the case period / Number treated in the control periods)

(95% confidence interval (CI): 1.36–2.49). Pregabalin, primidone, levetiracetam, tiagabine and zonisamide were not analyzed separately because of the minimal study discriminatory power due to the infrequent use of these drugs. Clonazepam (OR: 2.01, CI: 1.25–3.25), valproate (OR: 2.08, CI: 1.04–4.16), lamotrigine (OR: 3.15, CI: 1.35–7.34) and phenobarbital (OR: 1.96, CI: 1.02–3.75) were associated with a significantly increased risk of suicide. Furthermore, the results showed a trend towards lowered risk associated with the usage of carbamazepine and an increased risk with the usage of gabapentin.

Repeated analyses with use of both 15 and 60 days as case and control periods yielded similar results (data not shown).

Cox proportional-hazard analysis

From a total population of 4 614 807 individuals we identified 218 907 patients who claimed a prescription of an AED during the 10-year study period. We excluded all patients who were treated with an AED in 1996, hereby bringing the cohort down to 169 725 patients. Baseline characteristics are shown in Table 1. From the 670 suicides registered in the cohort we identified 268 patients who were in-treatment with an AED at the time of suicide, and 240 (90%) were only receiving one AED at this specific time.

The following covariates: age, socioeconomic status and Charlsons score, did not fulfil the model assumptions of linearity. Therefore, age was entered into the model as categorical covariates with five age groups, socioeconomic status with three groups and Charlsons score with four groups. There were no important interactions. Results from the three time intervals examined, i.e. 30, 90 and 180 days after initiation of a new AED, were comparable, but the most powered estimate emanated from the 180 days analysis. For sensitivity analyses we performed the same test with exclusion of patients who had a psychiatric diagnosis before patient inclusion or who received opiates at the time of inclusion, and we also performed a separate analysis of the subpopulation with a diagnosis of epilepsy. The results of these analyses showed the same statistical trends as those found in the main Cox analysis (data not shown). We also performed the Cox analysis with discharge from a psychiatric department ≤ 21 days as a time dependent covariate. This had limited effect on the results for the AEDs although it was an important risk factor for suicide (hazard ratio (HR): 8.27, CI: 6.23–10.98). The results from the Cox proportional-hazard analysis

Table 1. Baseline characteristics for AED treatment-naïve patients

Patients (mean age \pm SD)	169 725 (55.9 \pm 18.2)
Male (mean age \pm SD)	77 968 (54.6 \pm 17.8)
Female (mean age \pm SD)	91 757 (57.1 \pm 18.5)
Use of AEDs	
Gabapentin (%)	52 203 (30.8)
Carbamazepine (%)	31 801 (18.7)
Clonazepam (%)	27 971 (16.5)
Valproate (%)	24 255 (14.3)
Lamotrigine (%)	23 878 (14.1)
Oxcarbazepine (%)	18 392 (10.8)
Phenobarbital (%)	17 422 (10.3)
Pregabalin (%)	8792 (5.2)
Topiramate (%)	5544 (3.3)
Clobazam (%)	4097 (2.4)
Primidone (%)	1898 (1.1)
Phenytoin (%)	1642 (1.0)
Levetiracetam (%)	1601 (0.9)
Tiagabine (%)	73 (0.0)
Zonisamide (%)	35 (0.0)
Concomitant medication*	
Antidepressants (%)	64 951 (38.3)
Antipsychotics (%)	32 627 (19.2)
Anxiolytics (%)	54 817 (32.3)
Diagnosed epilepsy [†] (%)	4485 (2.6)
Diagnosed psychiatric disorder [†] (%)	36 453 (21.5)
Opiate analgesic treated [‡] (%)	53 999 (31.8)
Mean Charlsons score (\pm SD)	0.6 (\pm 1.3)

AED: antiepileptic drug.

*Claimed prescription ≤ 1 year prior first AED prescription claim.

[†]Diagnosed between 1978 and first AED prescription claim.

[‡]Claimed prescription ≤ 180 days prior to first AED prescription claim.

investigating the first 180 days of exposure are shown in Figure 2. The results for pregabalin, clobazam, tiagabine and zonisamide are not displayed because of insufficient study power. Clonazepam (HR: 2.72, CI: 1.77–4.17), valproate (HR: 2.40, CI: 1.42–4.05), lamotrigine (HR: 2.09, CI: 1.25–3.50), phenobarbital (HR: 3.71, CI: 2.30–5.99) and levetiracetam (HR: 5.91, CI: 1.46–23.91) all significantly increased the risk of suicide when compared to carbamazepine monotherapy as reference drug.

DISCUSSION

In the current study we examined the differences in the risk of suicide with the usage of various AEDs by two separate study designs, i.e. a case-crossover design and a historical cohort design. The results were essentially similar, with clonazepam, valproate, lamotrigine and phenobarbital being associated with increased risk of suicide in both analyses. In addition, levetiracetam showed increased risk of suicide in the cohort study, but this result was based on occurrence of only three suicides in the 180-day period and therefore had a wide CI.

ANTIEPILEPTIC DRUGS AND RISK OF SUICIDE

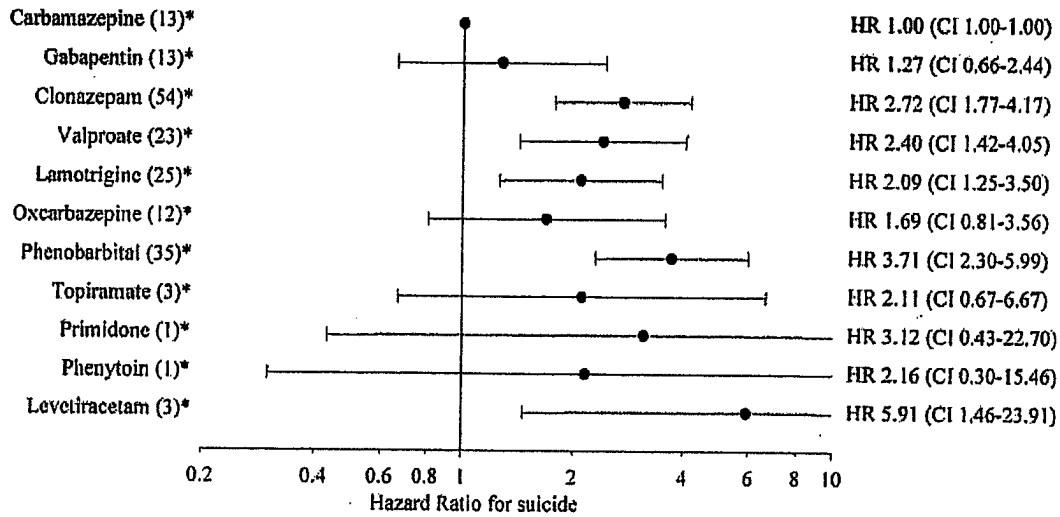


Figure 2. Results of the Cox proportional-hazard analysis with carbamazepine monotherapy as the reference drug. The analysis was adjusted for the following categorical covariates: age, sex, socioeconomic status, Charlsons score, civil status, diagnosis of epilepsy or a psychiatric disorder from 1978 to study inclusion, concomitant medication, and claimed prescription of opiate analgesics ≤ 180 days prior to study inclusion. The results for levetiracetam should be cautiously interpreted because of the limited sample size, hence lack of power for analysing this specific AED. * Suicides in the first 180 days of treatment

The case-crossover study demonstrated differences in the usage of AEDs in the case period shortly before the event, compared to two control periods prior in time but at most 120 days before the event. By using these two control periods we enhanced the robustness of the results of the case-crossover model. Hereby, the observed risks of suicide were linked to AED treatment initiation (and less frequently to AED discontinuation), rather than being associated with prolonged chronic treatment. For the cohort study we chose to analyze the first 180 days of treatment suggested by previous studies.^{5,7} Due to the exclusion of patients that were already receiving AEDs in 1996, 2.6% in the study cohort had diagnosed epilepsy at the time of their first AED prescription claim. Epilepsy is often a chronic disease and the majority of patients with epilepsy diagnosed before 1997 were therefore excluded from the cohort, i.e. a smaller part of the cohort had epilepsy than among random AED users, and AEDs used primarily for epilepsy therefore comprised a smaller fraction of the overall AED use in the cohort. The positive predictive value for the diagnosis of epilepsy is 81% in the Danish National Patient Register,¹⁶ and probably higher in the patients using AEDs. A larger proportion of the AED users than those diagnosed in the Danish National Patients Register have epilepsy. This is explained by a substantial number of individuals receiving the epilepsy diagnosis without ever being admitted to a hospital with this diagnosis. This was reflected by an additional 12% who were diagnosed with epilepsy after their first AED prescription.

Other studies

Previous cohort studies have found an association between the usage of phenobarbital and an increased risk of suicide in patients with epilepsy.^{17,18} This association was confirmed in the present study. On 31 January 2008, FDA issued a warning that all AEDs may increase the risk of suicidal behaviour or ideation, based on a meta-analysis of 199 placebo-controlled trials.⁷ The FDA conclusion was determined by an observed trend for increased risk of suicidal behaviour or ideation with nine of the eleven examined AEDs. Of note, only topiramate was associated with a significant increase in the risk of suicidal behaviour or ideation in all FDA analyses, whereas lamotrigine significantly increased the risk in a primary analysis, and carbamazepine lowered the risk of suicide. These findings are in agreement with the findings of the current study, where carbamazepine in the case-crossover study showed a trend for lower risk of suicide. In concordance with the FDA study conclusions, we also found increased risk of suicide with lamotrigine, and a weaker association with suicide was found for topiramate. The subgroup analyses of the FDA meta-analysis suggested that the risk of suicidal behaviour associated with AEDs was significantly increased in patients with epilepsy and not significantly so in patients with psychiatric diseases. We found no interaction between epilepsy and psychiatric disease, indicating that there was no significant difference in the suicide risk associated with AEDs between the two

groups. Our analysis was, however, limited by the fact that only 2.6% of the cohort had an epilepsy diagnosis registered in the National Patient Register.

Mechanisms

It has been suggested that depression and epilepsy share common pathogenetic mechanisms, and that some types of epilepsy cause higher risk of suicide than others.^{18,19} Such pathogenetic similarities may cause patients with epilepsy to have a higher prevalence of depression even before they develop epilepsy.⁸ In this respect, we found that AEDs increased the risk of suicide in the initiation phase of treatment, where patients could arguably have more depressive symptoms.

Different AEDs have different pharmacodynamic and pharmacokinetic effects that may influence their potential risk of suicide.^{20,21} For example, carbamazepine may elate the mood by increasing extracellular serotonin concentrations in the brain, which may play a role in the observed trend for lower risk of suicide with carbamazepine in our case-crossover study.^{22,23} Furthermore, phenobarbital, clonazepam, clobazam, valproate, gabapentin and tiagabine elevate gamma-aminobutyric acid (GABA) levels and potentiate the GABA-mediated inhibitory neurotransmission response, whereas levetiracetam reduce GABA levels.^{24,25} GABA impacts mood functions, but the different GABA-effectors act in different ways and do not necessarily have the same effect on the mood.²⁵ Many studies have claimed that valproate has a positive effect on the mood, but these findings are not consistent.^{26,27} It has also been suggested that the baseline mood state is important for the positive and negative psychiatric effects of AEDs, and that failure to observe these mechanisms may lead to safety concerns.²⁴ Whether such mechanism contributes to our findings remains to be determined, and further studies are needed to clarify the association between AEDs and suicide.

Strengths and limitations

The main strengths of the present study was the complete nationwide data, i.e. there was no selection bias related to e.g. age, gender, race, socioeconomic status or participation in private healthcare programs, and the accurate and complete registration of AED use in the National Prescription Register.

The main study limitation was the absence of available information on the therapeutic indication for treatment. Therapeutic indications for AEDs are not registered in the National Prescription Register, and include diseases

that are not adequately registered in the Danish National Patient Register. This limitation is reflected by the discrepancies between the total number of patients treated with AEDs and the sum of patients with epilepsy, psychiatric diseases and analgesic treatment (Table 1). Suicide is such a rare event that stratifying by drug dosage was not possible even with a population of the current size. Importantly, the majority of our study population was not registered with a diagnosis of epilepsy. However, the potential risk associated with AEDs may be inherent to the drug and thus similar for all patients irrespective of diagnosis. In addition, AEDs are used in multiple combinations, but in despite of its large sample size, our study did not have enough power to allow for further analyses of risk associated with AED combination therapy. Although previous suicide attempts are known to be important predictors of completed suicide, such attempts are not well registered and can therefore not be adjusted for.⁶

In the case-crossover design, each case was its own control. The short 30–120 day delay from the control period to the case period eliminated several confounders. Differences between the cases and the controls were their use of AEDs and any associated change in disease severity. It is notable that a substantial number of patients in the population used AEDs for other indications than epilepsy, and probably reinitiated their AED treatment in response to exacerbation of the underlying disease, e.g. psychosis or neuropathic pain. In these cases, an increased risk of suicide associated with the AED might be caused by confounding by indication and not by the drug.

Although the Cox proportional-hazard analysis applied on the cohort was adjusted for potential confounders, the effect of unmeasured confounders cannot be excluded. The increased risk for suicide found with various AEDs in patients without epilepsy are therefore subject to considerable uncertainty, but the validity of the results are strengthened by their relative correspondence with the data derived from the sensitivity analyses.

CONCLUSIONS

In the current nationwide register study, we found that clonazepam, valproate, lamotrigine and phenobarbital were associated with an increased risk of suicide in the treatment initiation phase.

CONFLICTS OF INTEREST

None of the authors has any conflict of interest to disclose.

KEY POINTS

- Antiepileptic drugs influence the risk of suicide after treatment initiation.
- In this study, the risk of suicide was increased with clonazepam, valproate, lamotrigine, and phenobarbital.

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